REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested. Claims 1-12 were pending. Applicants hereby cancel claims 9, 10, and 11. Claims 1, 7, 8, and 12 have been amended and new claims 13-21 have been added to prosecute certain specific embodiments of Applicants' invention. The above Amendments have been made without acquiescence to any rejection and without prejudice to prosecution of the removed or cancelled subject matter in a related divisional, continuation, or continuation-in-part application. Support for the amended and new claims may be found throughout the specification, for example, at page 7, lines 1-6; page 9, lines 20-25; page 10, lines 14-23; page 11, lines 7-28; and page 12, lines 21-27. The specification has been amended solely to update the cross-reference to related applications and to correct typographical errors. No new matter has been added to the application. Upon entry of this amendment, claims 1-8 and 12-21 will be pending.

Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

The Examiner rejected claims 1-12 under 35 U.S.C. § 112, first paragraph, alleging that the claimed subject matter is not enabled by the specification. The Examiner asserts that the disclosure in the specification is not commensurate with the scope of the claims. In particular, while the Examiner agrees that the specification enables a method of using a vaccine comprising an influenza hemagglutinin (HA) antigen, the Examiner asserts that the specification does not enable methods of using a vaccine comprising any influenza antigen.

Applicants respectfully traverse this rejection and submit that the specification enables a person skilled in the art to make and use, without undue experimentation, the claimed compositions and methods. Applicants submit, and the Examiner agrees, that claims directed to methods of treating an influenza infection or for eliciting an immune response to influenza using a vaccine comprising proteosomes and an influenza HA antigen are enabled by the specification.

Applicants, however, respectfully disagree with the assertion by the Examiner that the cited document, Crowe et al. (*Vaccine* 24:452-56 (2006)), suggests the unpredictability of making and using methods for eliciting an immune response to influenza by administering a

composition comprising proteosomes and any influenza antigen. Crowe et al. describe an immune response to a single peptide epitope (rather than a full-length polypeptide or multiple immunogenic epitopes) of each of three different influenza antigens when animals were vaccinated with dendritic cells pulsed with each of the peptides. Indeed, the document cautions, "it should be emphasized that the data presented in the current report pertain only to the specific epitopes and MHC haplotype described here" (*see* page 456, last paragraph). Moreover, the cited document lacks any teaching regarding an immune response to any one of these peptides when combined with proteosomes.

Nevertheless, solely to expedite prosecution of specific embodiments of Applicants' invention, the amended and new claims are directed, in pertinent part, to methods for eliciting an immune response against influenza and for treating an influenza infection in a subject, comprising administering a vaccine or composition that comprises proteosomes and an influenza hemagglutinin antigen. The specification provides abundant guidance, including working examples, that teach a person skilled in the art how to make and use these claimed methods, readily and without undue experimentation (*see, e.g.,* page 6, line 23 through page 7, line 10; page 8, line 28 through page 9, line 25; Examples 1-12).

Applicants, therefore, respectfully submit that the pending claims meet the requirements for enablement under 35 U.S.C. § 112, first paragraph, and respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 102

The Examiner rejected claims 1-4 and 6-12 under 35 U.S.C. § 102(b), asserting that the claims are anticipated by Levi et al. (*Vaccine* 13:1353-59 (1995)).

Applicants respectfully traverse this rejection and submit that the cited document fails to teach or suggest each and every feature of the amended claims. As an initial matter, Applicants submit that the rejection of claims 9-11 is rendered moot by the Amendments submitted herewith, which include cancellation of these claims without acquiescence of prejudice.

Levi et al. fail to teach or suggest a method to elicit an immune response against influenza in a subject by administering an influenza vaccine that comprises at least one influenza hemagglutinin (HA) antigen formulated with proteosomes in the substantial absence of detergent, wherein the formulation ratio of proteosomes to influenza HA antigen is *2:1 or greater*. Instead Levi et al. teach using a composition containing proteosomes and a lauroyl derivative of a single influenza HA peptide antigen at a ratio of *1:4* (*see* page 1354, column 2, Preparation of proteosomes-peptide vesicles: the peptide is mixed with proteosomes in 4:1 ratio). The cited document also fails to teach or suggest making and using a method for eliciting an immune response to influenza by administering a vaccine comprising at least one HA antigen and proteosomes wherein the vaccine is prepared by providing a mixture of at least one influenza HA antigen with a proteosome preparation in the presence of detergent, wherein the ratio of proteosomes to antigen is 2:1 or greater, followed by removing the detergent by diafiltration or ultrafiltration to obtain a proteosome-HA composition, which is then formulated into the vaccine. Levi et al. describe only a dialysis method for removing detergent from a composition comprising proteosomes and a lauroyl derivative of an influenza antigen peptide.

Thus, Applicants submit that the cited document fails to anticipate the amended and new claims and that these claims meet the novelty requirements under 35 U.S.C. § 102. Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claim 5 under 35 U.S.C. § 103(a), asserting that the claim is obvious over Levi et al. (*Vaccine* 13:1353-59 (1995)) as applied to claims 1-4 and 6-12, and further in view of Fynan et al. (*Int. J. of Immunopharmac.* 17:79-83 (1995)). The Examiner asserts that Levi et al. teach a method for eliciting an immune response against influenza, comprising administering a formulation of an influenza antigen and proteosomes. The Examiner states, however, that Levi et al. fail to teach or suggest intramuscular administration. The Examiner further asserts that Fynan et al. overcome this deficiency by teaching intramuscular administration of an influenza vaccine.

Applicants respectfully traverse this rejection and submit that the cited references, alone or in combination, fail to teach or suggest all claim limitations and fail to provide any teaching, suggestion, or motivation to combine or modify the teachings of the cited documents to achieve the claimed invention. Applicants further submit that a person having ordinary skill in the art would have no reasonable expectation of successfully achieving the claimed methods by combining the teachings of the cited references. Thus, the Examiner has not established a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d 1339, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (The PTO has the burden of showing a *prima facie* case of obviousness.).

As discussed above, Levi et al. fail to teach each and every feature of independent claim 1, from which claim 5 depends. Levi et al. fail to teach or suggest a method to elicit an immune response against influenza in a subject by administering an influenza vaccine that comprises at least one influenza hemagglutinin (HA) antigen formulated with proteosomes in the substantial absence of detergent, wherein the formulation ratio of proteosomes to influenza antigen is *2:1 or greater*. Instead Levi et al. teach administering a composition comprising proteosomes and a lauroyl derivative of a single influenza HA peptide antigen at a formulation ratio of *1:4* (*see* page 1354, column 2, Preparation of proteosomes-peptide vesicles: the peptide is mixed with proteosomes in 4:1 ratio). Furthermore, Levi et al. do not teach or suggest any alternative formulation.

Fynan et al. fail to remedy this deficiency. The cited reference fails to teach or suggest any antigen-proteosome formulation, but instead generally discusses various routes of administration of a DNA vaccine, which is a retroviral vector capable of expressing an influenza hemagglutinin antigen. Fynan et al. compare efficacy of inoculation with DNA when the DNA is delivered by inoculation in saline or by a gene gun. The results of such experiments are irrelevant to intramuscular immunization with a vaccine comprising proteosomes and the HA polypeptide, and a person having ordinary skill in the art would not reasonably expect that gene delivery methods would necessarily be applicable to administration of protein-based vaccines. Accordingly, a person having ordinary skill in the art would have no reasonable expectation of successfully obtaining a method comprising administration by an intramuscular route of a

vaccine comprising proteosomes and the influenza hemagglutinin polypeptide by combining the teachings of Levi et al. and Fynan et al.

Therefore, Applicants submit that the Examiner has not established a *prima facie* case of obviousness with respect to claim 5 and respectfully request that this rejection be withdrawn. Applicants further submit that all the amended and new claims submitted herewith meet the requirements for nonobviousness under 35 U.S.C. § 103.

Applicants respectfully submit that claims 1-8 and 12-21 are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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